

Could plant products bridge the gap for radioprotectors?

Prasan R Bhandari

Department of Pharmacology, S. D. M. College of Medical Sciences & Hospital, Sattur, Dharwad 580009, Karnataka, India

Corresponding to: Prasan R Bhandari, Associate Professor. Department of Pharmacology, S. D. M. College of Medical Sciences & Hospital, Sattur, Dharwad 580009, Karnataka, India. Email: prasangeeta2012@gmail.com.



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At the outset let me thank and congratulate the authors Prasanna PG *et al.* for comprehensively reviewing regarding radiation-induced injuries to skin, mucous membrane, lungs, and brain besides certain radioprotectors/mitigators in the article titled “Normal tissue protection for improving radiotherapy: where are the Gaps?” published in your esteemed journal in the month of June 2012 (1).

It was stated in the article that “Management of radiation-induced oral mucositis with drugs such as the radioprotector amifostine, KGF (keratinocyte growth factor, palifermin), benzydamine treatment, and other investigational therapies does not provide consistent results, as described below.”

In lieu of the above statement it would be worthwhile to mention that You WC *et al.* evaluated the effect of indigowood root (*Isatis indigotica*) on acute mucositis induced by radiation. The objective severity of mucositis, anorexia, and swallowing difficulty were measured before and after the treatment. Prophylactic application of IR consisted of gargling and then swallowing the IR preparation on the irradiated oral mucosa. The clinical trial showed that application of IR can reduce the severity of radiation mucositis (P=0.01), anorexia (P=0.002), and swallowing difficulty (P=0.002). Serum interleukin-6 was significantly lower in the IR group during the first, fifth, and seventh weeks. The investigators confirmed that indigowood root has anti-inflammatory ability to reduce the mucosal damage caused by radiation. The exact mechanisms and pathways still need further analysis (2).

However, the study incorporated only 20 patients; hence a larger study group should be evaluated to overcome this significant drawback of this study.

Additionally, it is a well-documented fact that topical aloe vera gel has been used for alleviating mild sunburns, frostbites, scalding burn, wound healing, mucous membrane protection and oral ulcers as well. The reported beneficial effects of topical aloe vera gel is presumably because of its anti-inflammatory, immunomodulatory, antifungal, free radical scavenging properties. Furthermore, it is demonstrated to increase collagen formation and inhibit collagenase. Hence, topical aloe

vera gel could be evaluated to mitigate the radiation-induced mucositis and candidiasis (3).

The authors Prasanna PG *et al.* also states aptly that “Protectors and mitigators, especially those intended for use in patients treated with radiotherapy, must be evaluated in relevant *in vitro* and *in vivo* systems to determine whether they also protect tumors or increase metastasis while protecting normal tissue or aiding normal tissue recovery. In addition, they should have limited normal tissue toxicity. The protective/mitigative effect of the candidate agents ideally should be determined using *in vivo* human orthotopic xenograft mouse models, where possible to demonstrate protection/mitigation in the target tissue, but not the tumor.”(1).

This would help to bridge the gaps in the search for an ideal radioprotector. As correctly pointed out the currently available and certain investigational synthetic radioprotectors have many drawbacks including high costs, side effects and toxicity. Thus innovative strategies are warranted to identify a potent and a safe radioprotector.

It is an acknowledged fact that the exposure to radiation would predominantly produce intracellular reactive oxygen species, leading to DNA strands breaks and conformational modifications of biomolecules. This will predictably cause damage to surrounding normal cells. Therefore, certain compounds/formulations might be envisaged to efficiently scavenge the free radicals and thus shield the surrounding normal cells from radiation induced injury.

Supporting the authors’ statement it could be suggested that the use of radioprotective compounds, like antioxidants, which selectively protect normal tissues against radiation injury will also permit use of higher doses of radiation to obtain better control and possible cure of cancers.

Certain approaches for the same include mimics of antioxidant enzymes, nitroxides, melatonin, growth factors, gene therapy, hyperthermia apart from natural products. The latter has several advantages since they are non-toxic with proven therapeutic benefits. As India and many Eastern countries have an enormous heritage of vast natural dietary and time tested medicinal resources it is worth exploring the

possibility of developing efficient, economically viable and clinically acceptable radioprotectors for human application from these resources (4).

In Ayurveda, the traditional Indian system of medicine, several plants have been used to treat free radical-mediated ailments and, therefore, it is logical to expect that such plants may also render some protection against radiation damage.

The prospects of antioxidants to decrease the cellular damage induced by ionizing radiation has been assessed in animal models for more than 50 years. Results from animal experiments suggest that antioxidant nutrients, such as vitamin E and selenium compounds, are protective against lethality and other radiation effects but to a lesser degree than most synthetic protectors. Some antioxidant nutrients and phytochemicals have the advantage of low toxicity although they are generally protective when administered at pharmacological doses. Naturally occurring antioxidants also may provide an extended window of protection against low-dose, low-dose-rate irradiation, including therapeutic potential when administered after irradiation. A number of phytochemicals, including caffeine, genistein, and melatonin, have multiple physiological effects, as well as antioxidant activity, which result in radioprotection *in vivo*. Many antioxidant nutrients and phytochemicals have antimutagenic properties, and their modulation of long-term radiation effects, such as cancer, needs further examination. In addition, further studies are required to determine the potential value of specific antioxidant nutrients and phytochemicals during radiotherapy for cancer (5).

Considerable information from pre-clinical studies suggests the usefulness of several plants and phytoconstituents in preventing the toxic effects of ionizing radiation at non-toxic concentrations. The plants with radioprotective effects include *Mentha piperita*, *Ocimum sanctum*, *Panax ginseng*, *Podophyllum hexandrum*, *Emblica officinalis*, *Tinospora cordifolia*, *Syzygium cumini*, *Zingiber officinale*, *Ageratum conyzoides*, *Aegle marmelos* and *Aphanamixis polystachya* (6).

Hazra B *et al.* too have reviewed some of the following plants for their prospective role in radioprotection: *Aloe arborescens*, *Azadirachta indica*, *Biophytum sensitivum*, *Boerhaavia diffusa*, *Citrus sinensis*, *Grewia asiatica*, *Moringa oleifera*, and *Punica granatum* (7).

A systematic screening approach can provide leads to identifying potential new candidate drugs from plant sources, for mitigation of radiation injury. The ultimate goal is to develop multidisciplinary expertise and therapeutic synergy between conventional and complementary therapies. Due to its abundance, low cost, and safety in consumption, these herbal/dietary radioprotectors have tremendous potential and countless possibilities for further investigation. It has the potential to develop as a non-toxic radioprotective agent, but only when gaps in the existing knowledge are bridged.

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